The ErbB3 receptor tyrosine kinase negatively regulates Paneth cells by PI3K-dependent suppression of Atoh1.

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Public Summary:
Paneth cells (PCs), a secretory population located at the base of the intestinal crypt, support the intestinal stem cells (ISC) with growth factors and participate in innate immunity by releasing antimicrobial peptides, including lysozyme and defensins. PC dysfunction is associated with disorders such as Crohn's disease and necrotizing enterocolitis, but the specific pathways regulating PC development and function are not fully understood. Here we tested the role of the neuregulin receptor ErbB3 in control of PC differentiation and the ISC niche. Intestinal epithelial ErbB3 knockout caused precocious appearance of PCs as early as postnatal day 7, and substantially increased the number of mature PCs in adult mouse ileum. ErbB3 loss had no effect on other secretory lineages, but increased expression of the ISC marker Lgr5. ErbB3-null intestines had elevated levels of the Atoh1 transcription factor, which is required for secretory fate determination, while Atoh1(+) cells had reduced ErbB3, suggesting reciprocal negative regulation. ErbB3-null intestinal progenitor cells showed reduced activation of the PI3K-Akt and ERK MAPK pathways. Inhibiting these pathways in HT29 cells increased levels of ATOH1 and the PC marker LYZ. Conversely, ErbB3 activation suppressed LYZ and ATOH1 in a PI3K-dependent manner. Expansion of the PC compartment in ErbB3-null intestines was accompanied with elevated ER stress and inflammation markers, raising the possibility that negative regulation of PCs by ErbB3 is necessary to maintain homeostasis. Taken together, our data suggest that ErbB3 restricts PC numbers through PI3K-mediated suppression of Atoh1 levels leading to inhibition of PC differentiation, with important implications for regulation of the ISC niche.

Scientific Abstract:
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